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TI Synthesis of brain-targeted 1-(2-deoxy-2-fluoro-beta-D-ribofuranosyl)-(E)-5-(2-iodovinyl)uracil coupled to a dihydropyridine dblarw pyridinium salt redox chemical-delivery system.
AU Morin, Kevin W.; Wiebe, Leonard I.; Knaus, Edward E. (1)
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SO Carbohydrate Research, (1993) Vol. 249, No. 1, pp. 109-116.
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DT Article
LA English
AB 1-(2-Deoxy-2-fluoro-beta-D-ribofuranosyl-(E)-5-(2-iodovinyl)uracil (**IVFRU**) was coupled to a dihydropyridine dblarw pyridinium salt redox chemical-delivery system (CDS) via a cleavable sugar-ester linkage as a site-directed approach to increase diffusion of the parent nucleoside into the central nervous system. Treatment of 1-(2-deoxy-2-fluoro-beta-D-ribofuranosyl)uracil with Bu-tMe-2SiCl in the presence of imidazole in DMF yielded the protected 5-O-tert-butyldimethylsilyl derivative. Subsequent reaction with nicotinoyl chloride hydrochloride in pyridine afforded 1-(5-O-tert-butyldimethylsilyl-2-deoxy-2-fluoro-3-O-(3-pyridylcarbonyl)-beta-D-ribofuranosyl)uracil. Reaction with iodine monochloride in methanol simultaneously cleaved the silyl ether moiety and iodinated the uracil ring at the 5-position. Coupling with (E)-Bu-3Sn-CH=CH-SiMe-3 in the presence of (Ph-3P)-2Pd-2(II)Cl-2 in THF gave 1-(2-deoxy-2-fluoro-3-O(3-pyridylcarbonyl)-beta-D-ribofuranosyl)-(E)-5-(2-trimethylsilylvinyl)uracil. Quaternization with iodomethane in acetone yielded the N-methylpyridinium iodide salt. Iodination of the reactive (E)-trimethylsilylvinyl moiety with iodine monochloride in acetonitrile and reduction of the quaternary pyridinium iodide salt with sodium dithionite in the presence of sodium hydrogen carbonate was carried out as a one-pot procedure to afford 1-(2-deoxy-2-fluoro-3-O-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-beta-D-ribofuranosyl)-(E)-5-(2-iodovinyl)uracil (**IVFRU**-CDS). This synthetic strategy is readily amenable to the high specific-activity radioiodination of **IVFRU**.

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18,14 W 771

TI Pharmacokinetics and metabolism of E-5-(2-[131I]iodovinyl)-2'-deoxyuridine in dogs.

AU Samuel J; Gill M J; Iwashina T; Tovell D R; Tyrrell D L; Knaus E E; Wiebe L I

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AB E-5-(2-Iodovinyl)-2'-deoxyuridine (**IVdU**) is a potent inhibitor of herpes simplex virus type 1 replication in vitro. The selective antiviral activity of **IVdU** is due to preferential phosphorylation by the herpes simplex virus type 1-encoded thymidine kinase. This selective sequesteration provided the rationale for the development of **radioiodinated IVdU** as a potential **radiopharmaceutical** compound for use in **noninvasive** diagnosis of herpes simplex virus encephalitis. We studied the pharmacokinetics and the in vivo metabolism of [131I]**IVdU** in dogs. The **radioactive** components in plasma were characterized and quantitated by **radio** high-pressure liquid chromatography. During incubation with dog blood, [131I]**IVdU** was metabolized to the corresponding base (E)-5-(2-iodovinyl)uracil. 131I-labeled (E)-5-(2-iodovinyl)uracil accounted for 73% of the total **radioactivity** present in plasma after 2 h of incubation, suggesting that phosphorolysis of the nucleoside is the major degradation pathway of **IVdU** in blood. The in vivo studies showed that there was an initial rapid clearance of the tracer from blood, followed by a second very slow clearance phase. Evaluation of the renal excretion of the **radiotracer** showed that only 8% of the injected dose was excreted by kidneys over an 8-h period. **IVdU** was rapidly metabolized to three **radioactive** compounds. Two of these metabolites, the base (E)-5-(2-iodovinyl)uracil and iodide, were characterized. The **radioactivity** associated with these metabolites was responsible for the slow clearance phase. Our results suggest that the development of [131I]**IVdU** as a **radiopharmaceutical** compound will require measures to prevent its rapid degradation in vivo.